Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials: authors' response

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Keywords: neutropenic sepsis, antimicrobials, β-lactams

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Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkl255
Advance Access publication 23 June 2006

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Sir,

Drs Rolston and Bodey1 have raised several points regarding our study, which we would like to address.

We compared broad-spectrum β-lactams currently recommended as first-line empirical monotherapy for febrile neutropenia in the latest Infectious Diseases Society of America (IDSA) guidelines, which include ceftazidime, cefepime, imipenem and meropenem.2 Indeed, our terminology (i.e. monotherapy) was inaccurate since we included studies that assessed combination therapy when vancomycin was added to both study arms.3 However, only 4 of the 33 included studies added vancomycin to all patients4,7 and 2 studies permitted the addition of vancomycin equally to both study arms when indicated.8,9 Exclusion of these studies does not change our results. Specifically, all-cause mortality with cefepime alone is significantly higher than the mortality with ceftazidime monotherapy (cefeplme versus ceftazidime RR 1.74, 95% CI 1.02–2.98, 6 studies, values >1 favour ceftazidime). Mortality is similar with ceftazidime and carbapenem monotherapy (ceftazidime versus carbapenems RR 1.10, 95% CI 0.65–1.86, 8 studies). All-cause mortality with cefepime monotherapy remains significantly higher when compared with other monotherapies combined (cefeplme versus others RR 1.52, 95% CI 1.07–2.14, 14 studies). Clinical failure results are identical to those presented in our publication. Our original objective was to guide clinicians in the selection of the type of the β-lactam used for monotherapy, or in combination with vancomycin when indicated.

Local resistance patterns should be used to guide treatment. Obviously, antibiotics that are not active given local epidemiology should not be used. The (external) validity of any study to the local settings must be considered before applying its conclusions.10 Drs Rolston and Bodey focus the interpretation of our results in light of the epidemiology at their centre. However ceftazidime may be used for monotherapy in locations where antibiotic resistance patterns permit its use.

Drs Rolston and Bodey quote the results of a meta-analysis comparing β-lactam monotherapies, showing ‘clear and statistically significant inferiority of ceftazidime’.11 This is not a systematic review, but a preliminary analysis of 25 randomized controlled trials ‘available in electronic databases’. This meta-analysis combined trials assessing β-lactam monotherapy and β-lactam-aminoglycoside combination therapy. The outcome reported by Glasmacher et al.11 is ‘response to the initial empirical antibiotic treatment without modification’ (opposite of treatment failure as defined in our study). Treatment failure in these trials is a composite endpoint driven mainly by modifications of the empirical treatment. Most of these trials were not blinded and treatment modifications were more common with ceftazidime when compared with a newer antibiotic. Comparability of study results is highly dependent on the definitions used in the study.12 The primary outcome on which our conclusions are based is all-cause mortality. This is also the main outcome for the patient. Other outcomes meaningful to patients include time to clinical response,13 need for invasive procedures, duration of hospital stay, but not treatment modification. Our study shows that cefepime was associated with significant higher all-cause mortality than comparators, despite its advantages in vitro. We cannot continue treating patients with an antibiotic that results in higher mortality unless the data, or our interpretation, are rebutted in a convincing way.

Should evidence be discarded because epidemiology has changed? Randomized controlled trials have paved the path to evidence-based treatment of febrile neutropenia. Current treatment is based on the earliest trials conducted by Dr Bodey and colleagues. Clinicians debating the type of monotherapy most appropriate for their locale should look at the evidence available. Appropriately conducted meta-analyses originating from systematic reviews enable unbiased integration of the evidence and assessment of patients’ safety. We believe that systematic reviews are a powerful tool to examine the evidence.14 The evidence should then be examined in the light of local patterns of pathogens and resistance at each medical centre. The applicability of results to specific settings should indeed be carefully considered.

Transparency declarations

We declare no conflict of interests.

References

The use of a particular test strain of *Staphylococcus aureus*.

The organism was deposited in the National Collection of Type Cultures (NCTC) in 1943 and assigned reference number NCTC 6571. In recognition of the fact that much of the early work on penicillin was carried out by workers in Oxford, *S. aureus* NCTC 6571 (cross-referenced in the American Type Culture Collection as ATCC 9144) has become known as the ‘Oxford Staphylococcus’.

The Oxford Staphylococcus is used widely in clinical diagnostic microbiology laboratories throughout the UK. It serves as a reference strain for antimicrobial susceptibility testing, being susceptible to antistaphylococcal antibiotics tested in such laboratories. It is also commonly used as a control organism for the phenotypic characterization of *S. aureus* including coagulase testing (regarded as a weak positive control) and determination of DNase activity.

The reference strain has been regarded as rather innocuous and safe to handle. However, through the ongoing programme of work to characterize reference strains and clinical isolates of *S. aureus* referred to the Staphylococcus Reference Unit (SRU, Centre for Infections, London), we have found that the Oxford Staphylococcus harbours the Panton-Valentine leucocidin (PVL) genes. This toxin has also been detected in a control strain of *S. aureus* used in the USA, isolated in Seattle in 1945 (ATCC 25923, NCTC 12981). PVL is regarded as a marker of virulence in *S. aureus*. It is strongly associated with skin and soft tissue infections (SSTIs) and published data suggest that where PVL genes are present they are expressed. The toxin induces pore formation in leucocytes, triggering the release of interleukins and other inflammatory mediators, leading to tissue necrosis and abscess formation. PVL-positive *S. aureus* have been circulating in the UK and causing disease for over 50 years. For example, phage type 80/81 strains prevalent in the 1950s and 1960s that caused a pandemic of community-acquired SSTIs, pneumonias and septicemias in children and young adults were PVL-positive.

Review of the SRU database has shown that among over 13,000 *S. aureus* isolates referred for typing and characterization from November 2003 to January 2006 15 have been identified as being closely related to the Oxford Staphylococcus by phage typing and/or PFGE. The majority (12 of 15; 80%) were referred as MRSA or coagulase-negative staphylococci, suggesting that the reference strain had been submitted, probably as a result of transposition errors occurring in the referring laboratory. The remaining three, however, were referred as MSSA recovered from patients with abscesses or community-acquired pneumonia, both of which are clinical presentations associated with PVL.

In these instances, it is likely that the organism referred was the aetiological agent. All three were unrelated temporally and occurred in geographically distinct areas of England. PCR- and DNA-sequence based analyses showed the clinical isolates were indistinguishable from each other and the Oxford Staphylococcus: they encoded PVL, enterotoxins G and I; were multilocus sequence type 30 (ST30); were protein A (*spa*) type t138; and belonged to accessory gene regulator (agr) allele group 3. All four cultures were susceptible to antistaphylococcal antibiotics (one clinical isolate was resistant to penicillin only) and PFGE profiles obtained by macro-restriction of chromosomal DNA with *Sma*I confirmed that they were closely related (Figure 1).

These data, together with previously published reports, show that representatives of this MSSA lineage continue to circulate in...